Neuron
Previews

Structure-Function Correlations in Stroke

K. Sathian[1,2,3,4,*] and Bruce Crosson[1,4,5]
[1]Department of Neurology
[2]Department of Rehabilitation Medicine
[3]Department of Psychology
Emory University, Atlanta, GA 30322, USA
[4]Rehabilitation R&D Center of Excellence, Atlanta VAMC, Decatur, GA 30033, USA
[5]Department of Psychology, Georgia State University, Atlanta, GA 30302, USA
*Correspondence: krish.sathian@emory.edu
http://dx.doi.org/10.1016/j.neuron.2015.02.031

A variety of behavioral deficits can result from stroke. In this issue of Neuron, Corbetta et al. (2015) report that the deficits tend to cluster into just a few sets and are mostly associated with subcortical damage disrupting inter-regional connectivity.

Stroke is a leading cause of global disability—in 2010, nearly 17 million people worldwide experienced their first stroke, while there were estimated to be 33 million survivors of stroke (Feigin et al., 2014). There is a vast literature detailing a veritable host of deficits resulting from stroke (for a review, see Ferro et al., 2010). Localization of the lesion based on careful neurological assessment is still a crucial part of the acute evaluation of stroke patients for early diagnosis and appropriate treatment, and it is also important at later stages for planning rehabilitative interventions (Sathian et al., 2011). However, some of the commonly held assumptions underlying presumed correlations between particular lesion locations and the associated behavioral deficits may be faulty. For instance, an almost axiomatic idea in behavioral neurology is the link between damage to a part of the left inferior frontal gyrus (Broca's area) and a specific language disorder known as Broca's aphasia, characterized by difficulty in production of language, as first described by Broca in 1861. Yet, the tightness of this link was called into question more than three decades ago when it was shown that the brain lesions in chronic Broca's aphasia extend far beyond the bounds of the left inferior frontal gyrus (Mohr et al., 1978). Indeed, a recent examination, using high-resolution magnetic resonance imaging (MRI) of the brains of the first two patients studied by Broca further highlights problems with the classic, "hypermodular" interpretation (Dronkers et al., 2007). These two patients had a particularly severe form of Broca's aphasia. Their brains revealed damage that involved a large part of the left hemisphere, not restricted to the cerebral cortical surface but extending deep into the white matter; moreover, the affected parts of the inferior frontal gyrus differed somewhat between these patients and were not entirely congruent with what is currently regarded as Broca's area. Thus, the authors of this study concluded that the extent of the damage and involvement of underlying white matter tracts, especially the superior longitudinal fasciculus (SLF), contributed to the profound language dysfunction experienced by Broca's first two patients (Dronkers et al., 2007).

The importance of white matter damage in mediating common behavioral deficits after stroke is clearly demonstrated in a report in this issue of *Neuron* by Corbetta et al. (2015) outlining a study of a fairly large sample of stroke survivors (n = 132) at about 2 weeks post-stroke. The vast majority of the lesions involved white matter, either exclusively or in addition to the cerebral cortex, based on high-resolution MRI. Thus, contrary to the belief that disconnection syndromes explain only a minority of post-stroke behavioral deficits, this report argues that they actually underlie the great majority. This is consistent not only with the findings of Dronkers et al. (2007) on the brains of Broca's index patients, but also with other recent work (e.g., observations that white matter disconnection is an important mediator of cognitive impairment following surgical resections for epilepsy) (Drane et al., 2015).

The study of Corbetta et al. (2015) went well beyond documenting the topography of stroke lesions. The authors undertook an impressive effort to assess a range of behavioral domains and their neural correlates, using sophisticated methods that included principal component analyses (PCAs) to identify factors that contributed significantly to the variance in each domain and the relationship between domains and ridge regression to map these behavioral domains onto the underlying neuroanatomy. Over three-fourths of the variance within the motor domain was explained by two factors associated with the left and right side of the body; a factor lateralizing to the left hemisphere accounted for a similar fraction of the variance in the language domain. Factors corresponding to visuospatial and verbal memory explained about two-thirds of the variance in the memory domain, while somewhat less variance was accounted for in the attention domain by three explanatory factors (contralesional visual field bias, sustained attention, and shifting attention). The overall conclusion from a subsequent step of across-domain PCA was that the behavioral deficits produced by strokes tend to aggregate into a fairly small number of associated sets. Three global factors emerged from the across-domain analyses: one non-lateralized factor associated with language, verbal memory, and, less strongly, spatial memory; a second, right-hemisphere-lateralized factor linked to left-sided motor performance and spatial memory; and a third, left-hemisphere-lateralized factor that

loaded on right-sided motor performance and attention shifting. Ridge regression revealed that each deficit was associated with multiple lesion loci, while lesion location explained higher variance for some deficits (e.g., left motor) than others (e.g., spatial memory), and lesion volume only accounted for a relatively small amount of variance. Regions associated with a multiplicity of deficits were mainly subcortical in the white matter and deep gray nuclei, with the number of deficits being proportional to the number of white matter tracts affected.

Among this interesting constellation of findings, some are intuitively appealing while others are not as easy to digest. For instance, the lateralization of factors explaining left- and right-sided motor performance seems straightforward. Spatial memory loaded on two of the factors, one associated with language and the other with left motor skill; although the authors did not explicitly consider the reason, this may be due to the hemispheric dichotomy between categorical and coordinate spatial processing, the left hemisphere being more important for categorical, and the right for coordinate spatial processing (Kosslyn, 1994). Conversely, the absence of lateralization of the language-related global factor is difficult to understand fully. Indeed, as discussed above, the within-domain language factor was clearly lateralized, suggesting that finer-grain analyses yield more specific associations. In agreement with this idea, language production and comprehension deficits were not separated by the language factor on the larger sample of 124 patients studied in this domain, while restriction of the analysis to a subset of aphasic patients, as defined based on scores at least 2 SD below the control mean, did tend to separate those with production and comprehension problems. Thus, the global factors may need to be regarded with caution pending further study, especially since the tests used for the different functional domains probably varied somewhat in their sensitivity.

Additional caveats are also in order. One is that the study of Corbetta et al. (2015) focused largely on a population of stroke survivors as would be admitted to a standard inpatient rehabilitation unit (i.e., with moderate functional problems rather than those on milder or more severe ends of the spectrum). Another issue is the relatively low proportion of patients with purely cortical lesions. Although the authors' analyses suggest that this subset did not differ from those with subcortical lesions, this bears further investigation. A third caveat is that some behavioral domains were omitted, particularly emotion and other socially relevant domains. Nevertheless, the authors are to be commended for their open acknowledgment of these limitations, which do not undermine the substantial contribution of their study. It is clear that further work will be necessary to resolve many open questions, but this should be taken as a positive rather than as a negative, in that this study will undoubtedly spawn future inquiry.

What mechanisms might explain the findings of this study? The authors consider, and discount, the possibility that diaschisis could be responsible. Diaschisis, a term originally introduced by von Monakow, refers to remote, circumscribed dysfunction triggered by a lesion, due to removal of inputs normally provided by connections from the lesioned to the target region (Carrera and Tononi, 2014). Corbetta et al. (2015) argue that this is incompatible with the observed profile of similar deficits resulting from lesions in varied loci and of different behavioral domains being associated with the same global factor. While these arguments are meritorious, we prefer to reserve judgment on this conclusion until the relevant neural circuits are understood in greater depth, particularly given the possibility that the global factors might be less robust than the within-domain factors (see above). In this context, it is worth noting that patients with acute, purely subcortical infarcts (perhaps excluding thalamic infarcts) rarely show aphasia or neglect unless the cortex is hypoperfused (Hillis et al., 2002)—an example of diaschisis. Certainly the authors' contention that their observations are probably based in disruptions of neural network connectivity makes good sense, and it fits with the growing recognition of the brain as a highly distributed system of neural networks (Sporns, 2010) and the increasing emphasis on neurologic disorders as being due to problems of network function (Stam, 2014). The notion of widespread disruptions in network connectivity has been referred to as "connectional diaschisis," as distinguished from the classic "focal diaschisis" (Carrera and Tononi, 2014).

The reduction in this study of structure-function correlations to just a few sets of associated deficits is broadly consistent with some recent factor analyses of the NIH Stroke Scale (e.g., Zandieh et al., 2012). It also resonates with everyday experience on the neurology wards, clinics, and rehabilitation units, where the nuances of neuroanatomical pedagogy "stroke by stroke" tend to recede into the background while the foreground is dominated by a generally common set of treatment and rehabilitative approaches. However, this line of thinking sets up obvious tension with the widely prevalent concept of variegated stroke syndromes that behavioral neurology and neuropsychology have been largely preoccupied with over the last century. So, how are these seemingly disparate viewpoints to be reconciled? It is important to appreciate that these apparently different schools of thought are distinguished by complementary approaches to the same problem: while the classical approach relied strongly on individual case studies, many of which were masterly models of elegance, and studies of patients with specific functional disorders, the study of Corbetta et al. (2015) and related approaches focus on what is common across individuals of the population. In our view, both these approaches will continue to be valuable, and the full picture will probably require intelligent fusion of the data emerging from examination at multiple levels of granularity. And perhaps to the chagrin of current trainees, the clinical neurobehavioral evaluation is not yet slated for demise in our brave new world.

REFERENCES

Carrera, E., and Tononi, G. (2014). Brain *137*, 2408–2422.

Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, C.D., et al. (2015). Neuron *85*, this issue, 927–941.

Drane, D.L., Loring, D.W., Voets, N.L., Price, M., Ojemann, J.G., Willie, J.T., Saindane, A.M., Phatak, V., Ivanisevic, M., Millis, S., et al. (2015). Epilepsia *56*, 101–113.

Dronkers, N.F., Plaisant, O., Iba-Zizen, M.T., and Cabanis, E.A. (2007). Brain *130*, 1432–1441.

Feigin, V.L., Forouzanfar, M.H., Krishnamurthi, R., Mensah, G.A., Connor, M., Bennett, D.A., Moran, A.E., Sacco, R.L., Anderson, L., Truelsen, T., et al.; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group (2014). Lancet *383*, 245–254.

Ferro, J.M., Martins, I.P., and Caeiro, L. (2010). Behavioral neurology of stroke. In Textbook of Stroke Medicine, M. Brainin and W.-D. Heiss, eds. (Cambridge, UK: Cambridge University Press), pp. 178–202.

Hillis, A.E., Wityk, R.J., Barker, P.B., Beauchamp, N.J., Gailloud, P., Murphy, K., Cooper, O., and Metter, E.J. (2002). Brain *125*, 1094–1104.

Kosslyn, S.M. (1994). Image and Brain. The Resolution of the Imagery Debate. (Cambridge, MA: MIT Press), pp. 191–245.

Mohr, J.P., Pessin, M.S., Finkelstein, S., Funkenstein, H.H., Duncan, G.W., and Davis, K.R. (1978). Neurology *28*, 311–324.

Sathian, K., Buxbaum, L.J., Cohen, L.G., Krakauer, J.W., Lang, C.E., Corbetta, M., and Fitzpatrick, S.M. (2011). Neurorehabil. Neural Repair *25* (*Suppl*), 21S–32S.

Sporns, O. (2010). Networks of the brain. (Cambridge, MA: MIT Press).

Stam, C.J. (2014). Nat. Rev. Neurosci. *15*, 683–695.

Zandieh, A., Kahaki, Z.Z., Sadeghian, H., Pourashraf, M., Parviz, S., Ghaffarpour, M., and Ghabaee, M. (2012). Int. J. Neurosci. *122*, 140–144.

Intersectional Illumination of Neural Circuit Function

William E. Allen[1,2] and Liqun Luo[1,2,3,*]
[1]Neurosciences Program
[2]Department of Biology
[3]Howard Hughes Medical Institute
Stanford University, Stanford, CA 94305, USA
*Correspondence: lluo@stanford.edu
http://dx.doi.org/10.1016/j.neuron.2015.02.032

In this issue of *Neuron*, Madisen et al. (2015) report the construction of several new transgenic mouse lines that apply intersectional genetic tools to achieve high levels of expression and cell-type specificity, providing a useful resource for future studies.

The development of molecular tools to anatomically map, functionally manipulate, and record the activity of genetically defined subpopulations of neurons has revolutionized neuroscience (Luo et al., 2008). It is now possible in a variety of organisms to deconstruct complex neural circuits into their constituent components and to study each part's anatomy, physiology, and function in isolation. Many neuroscientists believe that this reductionist approach will result in a mechanistic understanding of how brains compute, learn, and produce behavior. A necessary component of this approach is methods to target the expression of genes encoding these molecular tools to specific groups of neurons.

The most common method is to inject viral vectors that encode molecular tools. In the mouse, this is often used in conjunction with transgenic lines that express the site-specific recombinase Cre in specific cell populations. While offering high-level expression and spatial control, virally delivered tools suffer from several problems that can introduce significant uncontrolled variability into experiments: it is difficult even with stereotactic surgery to repeatedly infect exactly the same population of cells; viral titer varies from batch to batch, affecting the efficacy of infection and expression; and long-term viral infection may affect cell health. One solution to these problems is the use of transgenic mouse lines that heritably express a molecular tool in a specific pattern.

The simplest approaches use a genomic locus or promoter to directly express a molecular tool in a specific spatiotemporal pattern as a one-component transgenic (Table 1, left). Different approaches to generating one-component transgenic lines trade off simplicity for specificity. The simplest approach uses zygotic pronuclear microinjection of recombinant DNA that is then randomly integrated into the genome as a transgene with variable copy numbers. The transgene can contain just a short promoter or enhancer sequence directly driving a molecular tool gene or a more complex bacterial artificial chromosome (BAC) containing a molecular tool gene embedded in an endogenous gene's *cis*-regulatory elements to better mimic that gene's expression pattern (Gong et al., 2003). The most specific but also most labor-intensive method reproduces endogenous expression patterns by knocking the coding sequence of a molecular tool into single genomic loci through homologous recombination in embryonic stem (ES) cells.

One-component approaches suffer from several drawbacks. A major problem is the lack of flexibility: a separate mouse line has to be generated for each combination of molecular tool and targeted cell type. In addition, the endogenous *cis*-regulatory elements surrounding the transgene have a strong effect on the transgene's cell-type specificity, regulability,